Attachment A

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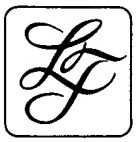
THIRD EDITION

Principles of Medicinal Chemistry



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who have taken as few as one to two doses of suprofen. If flank pain occurs, suprofen should be discontinued and renal function monitored."

Suprofen, brand-named Suprol, available as 200 mg capsules, has a recommended dosage in adults of 200 mg every 4 to 6 hours as needed, up to a maximum of 800 mg per day.

Structure-Activity Relationships

Suprofen is bioisosteric with ketoprofen in possessing the para-thenoyl substituent rather than the m-benzoyl of ketoprofen. In SAR of the suprofen molecule, thiophene as heterocycle and methyl as the α-alkyl substituents on the acetic acid moiety were clearly optimal. The thiazole and pyrimidine derivatives were less active. Replacement of the carboxyl group by amide or anilide gave less potent compounds, while the tert-amino-containing ester substitutions resulted in potent activity.[30] Suprofen is approximately six times as potent as ketoprofen.

Naphthaleneacetic Acid Derivatives

Naproxen, U.S.P.

Naproxen is an anti-inflammatory arylpropionic acid introduced in 1976, and ranked among the top 15 drugs in number of prescriptions filled in 1985.

Naproxen is an acidic, highly albumin-bound drug. After oral administration, it is promptly and fully absorbed. The mean half-life of the drug is 13 hours, close to ideal for twice-daily administration. The only metabolite detected in man is the 6-desmethylnaproxen. Both it and naproxen itself are excreted in the urine, primarily as conjugates, the glucuronide being the most prevalent. Naproxen, like most other acidic nonsteroidal anti-inflammatory agents, inhibits prostaglandin synthesis; this is the most probable mechanism of action.

In experimental animals, Naproxen shows anti-inflammatory activity 11 times that of phenylbutazone and analgesic and antipyretic activities 7 times and 22 times those of aspirin, respectively. Naproxen is indicated for relief of the signs and symptoms of rheumatoid arthritis. A comparison of 2.4 g of fenoprofen daily, 2.4 g ibuprofen daily, and 750 mg naproxen daily in treatment of rheumatoid arthritis has shown naproxen to have the greatest antirheumatic activity, strongest patient preference, and lowest incidence of side effects. Similar results were seen in comparing 500 mg of naproxen daily and 3.6 g of aspirin daily. Naproxen is also effective in clinical treatment of osteoarthritis, ankylosing spondylitis, acute gout, tendinitis and bursitis, primary dysmenorrhea, and in the relief of mild to moderate pain.

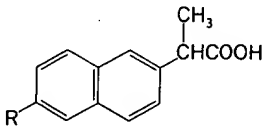
Preparations Available

Naproxen, also called Naprosyn or (+)6-methoxy-α-methyl-2-naphthaleneacetic acid, is available in 250 mg tablets for oral administration. Naproxen, a while crystalline substance, is lipid-soluble, practically insoluble in water at low pH, and freely soluble in water at high pH. The recommended starting dose of naproxen in rheumatoid arthritis is 250 mg orally, twice daily (morning and evening). Daily doses above 750 mg are not recommended.

Also marketed is the levorotatory naproxen sodium Anaprox or sodium (−) 6-methoxy-α-methyl-2-naphthaleneacetate, in film-coated tablets of 275 mg, equivalent to about 250 mg of naproxen. Both naproxen sodium and naproxen circulate in plasma as the identical dextrorotatory naproxen anion. Absorption is claimed to be more rapid with the sodium salt, which has led to its development as an analgesic. The recommended doses and indications for naproxen and naproxen sodium are similar.

Structure-Activity Relationships

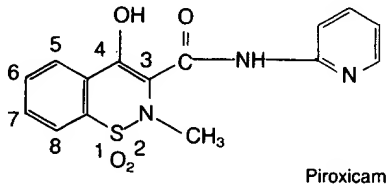
Naproxen was designed to include the chemical features found in the preexisting anti-inflammatory drugs; i.e., an aromatic group, an acidic group, and a side chain, but not to contain a nitrogen atom, which may be responsible for some of the observed side effects. Modification of the side chain R on the naphthalene ring showed that the 6-position was the most active with lessened effects at other positions. Also, when the side chain R is larger than OCH_3 or SCH_3, activity was again reduced. The carboxyl group may be replaced by alcohol and aldehyde functions and retain activity. Naproxen, a dextrorotatory compound, was obtained from the racemic form by use of cinchonidine.



Enolic Acids—Oxicams

Piroxicam, U.S.P.

A new class of nonsteroidal anti-inflammatory compounds that are not carboxylic acids is exemplified by the potent agent piroxicam (Feldene), 4-hydroxy - 2 - methyl - N - 2 - pyridyl - 2[H] - 1,2-benzothiazine-3-carboxamide 1,1-dioxide. Piroxicam is a member of a broad series now referred to as oxicams (4-hydroxy-1,2-benzothiazines).



Piroxicam

Piroxicam is acidic through the enolic 4-hydroxy substituent and has a pKa of 6.3 when measured in 2:1 dioxane-water as solvent. This acidity was partially attributed to a hydrogen-bonded stabilization of a planar enolate anion as shown in structure A. In addition to A, some contributions from

Roche

B

EC-NAPROSYN® (naproxen) Delayed-Release Tablets

NAPROSYN® (naproxen) Tablets

ANAPROX®/ANAPROX® DS (naproxen sodium) Tablets

NAPROSYN® (naproxen) Suspension

This product information is intended for United States residents and on-screen viewing only.
Before prescribing, please refer to printed complete product information.

Complete Product Information

Roche

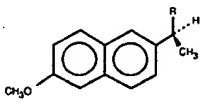
R_x only

EC-NAPROSYN® (naproxen) Delayed-Release Tablets
NAPROSYN® (naproxen) Tablets
ANAPROX®/ANAPROX®DS (naproxen sodium) Tablets
NAPROSYN®(naproxen) Suspension

DESCRIPTION

Naproxen is a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs.

The chemical names for naproxen and naproxen sodium are (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid and (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid, sodium salt, respectively. Naproxen and naproxen sodium have the following structures, respectively:



naproxen	(R=-COOH)	$C_{14}H_{14}O_3$	mol wt 230.26
naproxen sodium	(R=-COONa)	$C_{14}H_{13}NaO_3$	mol wt 252.23

Naproxen is an odorless, white to off-white crystalline substance. It is lipid-soluble, practically insoluble in water at low pH and freely soluble in water at high pH. The octanol/water partition coefficient of naproxen at pH 7.4 is 1.6 to 1.8. Naproxen sodium is a white to creamy white, crystalline solid, freely soluble in water at neutral pH.

NAPROSYN (naproxen) Tablets contain 250 mg, 375 mg or 500 mg of naproxen and croscarmellose sodium, iron oxides, povidone and magnesium stearate.

EC-NAPROSYN (naproxen) Delayed-Release Tablets are enteric-coated tablets containing 375 mg or 500 mg of naproxen and croscarmellose sodium, povidone and magnesium stearate. The enteric coating dispersion contains methacrylic acid copolymer, talc, triethyl citrate, sodium hydroxide and purified water. The dispersion may also contain simethicone emulsion. The dissolution of this enteric-coated naproxen tablet is pH dependent with rapid dissolution above pH 6. There is no dissolution below pH 4.

Each ANAPROX 275 mg and ANAPROX DS 550 mg tablet contains naproxen sodium, the active ingredient, with magnesium stearate, microcrystalline cellulose, povidone and talc. The coating suspension for the ANAPROX 275 mg tablet may contain hydroxypropyl methylcellulose 2910, Opaspray K-1-4210A, polyethylene glycol 8000 or Opadry YS-1-4215. The coating suspension for the ANAPROX DS 550 mg tablet may contain hydroxypropyl methylcellulose 2910, Opaspray K-1-4227, polyethylene glycol 8000 or Opadry YS-1-4216.

NAPROSYN (naproxen) Suspension for oral administration contains 125 mg/5 mL of naproxen in a vehicle containing sucrose, magnesium aluminum silicate, sorbitol solution and sodium chloride (30 mg/5 mL, 1.5 mEq), methylparaben, fumaric acid, FD&C Yellow No. 6, imitation pineapple flavor, imitation orange flavor and purified water. The pH of the suspension ranges from 2.2 to 3.7.

CLINICAL PHARMACOLOGY

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The sodium salt of naproxen has been developed as a more rapidly absorbed formulation of naproxen for use as an analgesic. The naproxen anion inhibits prostaglandin synthesis but beyond this its mode of action is unknown.

Pharmacokinetics: Naproxen itself is rapidly and completely absorbed from the gastrointestinal tract with an in vivo bioavailability of 95%. The different dosage forms of NAPROSYN are bioequivalent in terms of extent of absorption (AUC) and peak concentration (C_{max}); however, the products do differ in their pattern of absorption. These differences between naproxen products are related to both the chemical form of naproxen used and its formulation. Even with the observed differences in pattern of absorption, the elimination half-life of naproxen is unchanged across products ranging from 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days, and the degree of naproxen accumulation is consistent with this half-life. This suggests that the differences in pattern of release play only a negligible role in the attainment of steady-state plasma levels.

Absorption:

Immediate Release: After administration of NAPROSYN tablets, peak plasma levels are attained in 2 to 4 hours. After oral administration of ANAPROX, peak plasma levels are attained in 1 to 2 hours. The difference in rates between the two products is due to the increased aqueous solubility of the sodium salt of naproxen used in ANAPROX. Peak plasma levels of naproxen given as NAPROSYN Suspension are attained in 1 to 4 hours.

Delayed Release: EC-NAPROSYN is designed with a pH-sensitive coating to provide a barrier to disintegration in the acidic environment of the stomach and to lose integrity in the more neutral environment of the small intestine. The enteric polymer coating selected for EC-NAPROSYN dissolves above pH 6. When EC-NAPROSYN was given to fasted subjects, peak plasma levels were attained about 4 to 6 hours following the first dose (range: 2 to 12 hours). An in vivo study in man using radiolabeled EC-NAPROSYN tablets demonstrated that EC-NAPROSYN dissolves primarily in the small intestine rather than the stomach, so the absorption of the drug is delayed until the stomach is emptied.

When EC-NAPROSYN and NAPROSYN were given to fasted subjects (n=24) in a crossover study following 1 week of dosing, differences in time to peak plasma levels (T_{max}) were observed, but there were no differences in total absorption as measured by C_{max} and AUC:

Latest Updated:2001-01-01 22:53(GMT+08:00) Taichung

Composing and Editing by Huang Cheng-Yuan, Pharm.

¡@

Noyan Tablets 375mg "Weidar"

¡@

[Compositions]¡G Each Tablet Contains:
Naproxen.....375mg

[Clinical Pharmacology]:
1.NOYAN is a nonsteroidal anti-inflammatory drug. Naproxen inhibits prostaglandin synthesis with analgesic properties.
NOYAN is rapidly and completely absorbed from the GI tract. After administration of NOYAN, peak plasma levels are attained in 2 to 4 hours, with steady-state conditions normally achieved after 4-5 doses. The mean hal-life is approximately 13 hours, and it is greater than 99% albumin bound. Approximately 95% of the dose is excreted in the urine, primarily as naproxen, 6-0-desmethyl naproxen or their conjugates. The drug does not induce metabolizing enzymes.

2.The drug in clinical use for following patients: Osteoarthritis, rheumatoid arthritis, juvenile arthritis, ankylosing spondylitis, tendinitis, bursitis and acute gout.
Improvement in patients treated:
For osteoarthritis: To reduce joint pain or tenderness, increase in range of motion in knee joints and increase mobility.
For rheumatoid arthritis: To reduce joint swelling, pain and duration of morning stiffness. Increasing mobility.
For ankylosing spondylitis: To decrease night pain, morning stiffness and pain at rest. In double-blind studies the drug was shown to be as effective as aspirin, but with fewer side
effects.
For acute gout: A favorable response to the drug was shown by significant clearing of inflammatory changes (e.g., decrease in swelling,heat) within 24-48 hours, as well as by relief of pain and tenderness.

3.The drug drug has been shown to be comparable to aspirin and indomethacin in patients with rheumatoid arthritis, osteoarthritis, and juvenile arthritis, the frequency and severity of the milder GI adverse effects and CNS adverse effects were less than in both the aspirin- and indomethacin-treated patients.

4.The drug may be used safely in combination with gold salts and/or corticosteroids. When added to the regimen of patients receiving corticosteroids it did not appear to cause greater improvement over that seen with corticosteroids alone. When added to the regimen of patients receiving gold salts the drug did result in greater improvement.

5.The drug was studies in patients with mild to moderate pain, and pain relief was obtained within 1 hour. It is not a narcotic and is not a CNS-acting drug. Controlled double-blind studies have demonstrated the analgesic properties of the drug in, for example, post-operative, post-partum, orthopedic and uterine contraction pain and dysmenorrhea. In dysmenorrheic patients, the drug reduces the level of prostaglandins in the uterus, which correlates with a reduction in the frequency and severity of uterine contractions.

[Indications]:
Osteoarthritis, rheumatoid arthritis, juvenile arthritis, ankylosing spondylitis, tendinitis, bursitis and acute gout. Primary dysmenorrhea, relief of mild to moderate pain.

[Dosage and Administration]¡G
Adult:1 tablet 2 times daily (morning and evening).
The dose may be adjusted up or down depending on the clinical respone of the patient. Symptomatic improvement in arthritis usually begins within 2 weeks. However, if improvement is not seen within this period, a trial for an additional 2 weeks should be considered.
Children: for juvenile arthritis, 1/2 tablet 2 times daily (10mg/kg/day).
Acute gout:Starting dose is 2 tablets, follwed by 1 tablet every 8 hours until the attack has subsided.
Use only on prescription by physician.

[Contraindications]:
1.Hypersensitivity.
2.It is contraindicated in patients in whom aspirin or other NSAIDs induce the syndrome of asthma, rhinitis, and nasal polyps. Careful questioning of patients for such things as asthma, nasal polys, urticaria, and hypotension associated with NSAIDs before starting therapy is important. If such symptoms occur during therapy, treatment should be discontinued.

[Warning]:
NSAIDs including naproxen may be induced GI bleeding, ulceration. Caution should be used if patients with history of GI events.

[Precautions]:
1.Naproxen should not be used concomitantly with the related drug naproxen sodium since they bothcirculate in plasma as the naproxen anion.

2.Naproxen and its metabolites are eliminated primarily by the kindney, therefore the drug should be used with great caution in patients with significantly impaired renal function and the monitoring of serum creatinine. Caution should be used if the drug is given to patients with creatinine clearance of less than 20mL/min because accumulation of naproxen metabolites has been seen in such patients. Long-term administration of naproxen has resulted renal dysfunction (nephritis, renal papillary necrosis or the reduction in renal b;ood flow). Peripheral edema has been observed in some patients. For this reason, the drug should be used with caution in patients with fluid retention, hypertension or heart failure.

3.The unbound plasma fraction of naproxen is increased in the elderly. It is prudent to use the lowest effective dose in the elderly.

4.A two-year study was performed in rats to evaluate the carcinogenic potential of the drug. No evidence of carcinogenicity was found.

5.Animal studies has shown to no evidence of harm to the fetus due to the drug. No adequate and well-controled studies in pregnant women, so the drug should not be used during pregnancy unless clearly needed.

6.The naproxen anion has been found in the milk of lactating women at a concentration of approximately 1% of that found in the plasma, usein nursing mothers should be avoided.

[Adverse reactions]:
The most frequent adverse reactions greater than 1%:
GI: Constipation, heartburn, abdominal pain, nausea, dyspepsia, diarrhea, stomatitis.
CNS: Headache, dizziness, drowsiness.
Dermatologic: Itching, skin eruptions, ecchymoses, sweating, purpura.
Special senses: Hearing disturbances, visual disturbances.
Cardiovascular: Edema, Palpitations, dyspnea.
General: Thirst.

[Overdose]:
Significant overdosage may be characterized by drowsiness, heartburn, indigestion, nausea or vomiting. It is not known what dose of the drug would be life threatening. Should a patient ingest a large number of tablets, accidentally or purposefully, the stomach may be emptied and usual supportive measures employed. Charcoal was effective in reducing plasma levels of naproxen. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding.

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Attachment D

Gut ONLINE

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GUT 1997;**41**:344-353 (September)

Mitochondrial damage: a possible mechanism of the "topical" phase of NSAID induced injury to the rat intestine

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Abstract

Background—The "topical" effect of non-steroidal anti-inflammatory drugs (NSAIDs) seems to be an important cause of NSAID induced gastrointestinal damage.
Aim—To examine the possible mechanism of the "topical" phase of damage in the small intestine.
Methods—Electron microscopy and subcellular organelle marker enzyme studies were done in rat small intestine after oral administration of indomethacin (doses varied between 5 and 30 mg/kg). The effect of conventional and non-acidic NSAIDs on rat liver mitochondrial respiration was measured in vitro in a Clarke-type oxygen electrode.
Results—The subcellular organelle marker enzymes showed mitochondrial and brush border involvement within an hour of indomethacin administration. Electron microscopy showed dose dependent mitochondrial changes following indomethacin administration consistent with uncoupling of oxidative phosphorylation (or inhibition of electron transport) which were indistinguishable from those seen with the uncoupler dinitrophenol. Parenteral indomethacin caused similar changes, but not in rats with ligated bile ducts. A range of NSAIDs, but not paracetamol or non-acidic NSAIDs which have a favourable gastrointestinal tolerability profile, uncoupled oxidative phosphorylation in vitro at micromolar concentrations and inhibited respiration at higher concentrations. In vivo studies with nabumetone and aspirin further suggested that uncoupling or inhibition of electron transport underlies the "topical" phase of NSAID induced damage.
Conclusion—Collectively, these studies suggest that NSAID induced changes in mitochondrial energy production may be an important component of the "topical" phase of damage induction.
(*GUT* 1997;**41**:344-353)

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- Abstract
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- Material and Methods
- Results
- Discussion
- References

Keywords: intestinal inflammation; intestinal toxicity; mitochondrial function; drug induced toxicity

centrifuged at 500 *g* for 10 minutes and the resulting supernatant re-centrifuged at 12 000 *g* for 10 minutes. The pellet was resuspended in the sucrose solution and centrifuged for 10 minutes at 12 000 *g* to give the resulting mitochondrial enriched pellet used for these experiments. All procedures were performed at 4°C.

Oxygen consumption was measured in a Clarke-type oxygen electrode, as described previously.[24] The reaction mixture consists of 150 mM sucrose, 10 mM potassium chloride, 5 mM magnesium chloride, and 1 mM potassium dihydrogen orthophosphate in 10 mM HEPES-NaOH buffer, pH 7.4. Substrates, inhibitors and drugs were introduced into the chamber (1.0 ml capacity) by syringe and reactions were carried out at 30°C under magnetic stirring.

Electron transport experiments were done with mitochondria after addition of 0.1 mM cyanide p-(trifluoromethoxy) phenylhydrazone (FCCP) prior to the addition of the drugs.

Rotenone and FCCP were dissolved in ethanol whereas the rest were solubilised in 10% DMSO prior to dilution and pH adjusted to 7.4. The solvent was used by itself in the control experiments. The chemical structures of the drugs used in these experiments are shown in fig 1. The conventional NSAIDs studied were indomethacin (pKa 4.5), naproxen (pKa 4.2), aspirin (pKa 3.5), flurbiprofen (pKa 4.2), and piroxicam (pKa 6.3); paracetamol was studied as a non-NSAID analgesic control. Three non-acidic NSAIDs were also studied: nabumetone (and its active acidic metabolite 6-methoxy-2-naphthylacetic acid (6-MNA; pKa 4.5)) and two chemical modifications of flurbiprofen, namely NO-flurbiprofen (fig 1), a nitroxybutylester derivative of flurbiprofen, and a flurbiprofen dimer where a molecule of flurbiprofen is linked to another flurbiprofen molecule via an acid anhydrite bond. Each drug was tested over a range of concentrations and the data presented represent the mean of three to five experiments performed on different days.

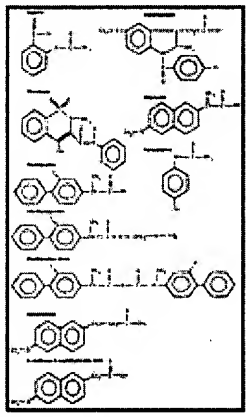

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Figure 1 : *Chemical structure of the NSAIDs and paracetamol used in the study.*

Mitochondrial protein was measured by using Pierce's BCA protein assay kit, using bovine serum albumin as standard protein.

BILE DUCT LIGATION EXPERIMENTS

Pharmacokinetics permits three possible routes by which NSAIDs may come into contact with the small intestinal mucosa. Firstly, the "topical" phase following ingestion (during absorption), secondly, a systemic route as the drug enters the vascular compartment and is distributed throughout the body, and, thirdly, following excretion in bile which may re-expose the small intestine to the "topical" phase. In an attempt to discriminate between the "topical" effects of indomethacin on intestinal mitochondrial morphology and the systemically mediated effect, one group of rats underwent bile duct ligation while the other underwent sham operation (all animals were re-fed after the procedure). Twenty four hours later, after an overnight fast, the animals received indomethacin 20 mg/kg